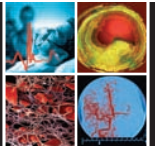




HYPERTENSION MANAGEMENT IN ACUTE NEUROVASCULAR EMERGENCIES



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OBJECTIVES:

1. Describe the rationale for lowering blood pressure in hypertensive neurovascular emergencies.
2. Describe the potential harm in lowering blood pressure in hypertensive neurovascular emergencies.
3. Define the agents of choice in managing hypertensive neurovascular emergencies.

INTRODUCTION

Management of blood pressure in the setting of neurovascular emergencies is of considerable concern to emergency physicians. It is an area of medicine with remarkably little clinical trial data from which to derive evidence-based treatment approaches. Thus, clinicians must rely on an understanding of the underlying pathophysiology and the mechanism of action of therapeutic agents to drive treatment decisions.

When treating patients with neurovascular emergencies and hypertension, two competing concerns must be balanced. The first is the concern that acutely elevated blood pressure can lead to injury in multiple vascular beds, including hemorrhage in the brain and elsewhere. The second is the concern that reduction of blood pressure can compromise tissue with marginal perfusion. Factors that must be considered in deciding whether to lower the patient's blood pressure, and if so to what degree, include 1) the type of neurovascular emergency, 2) the level of hypertension, 3) the patient's past blood pressure history, and 4) the perceived condition of the patient's native autoregulatory system.

The three types of neurovascular emergencies that will be considered here are acute ischemic stroke, intracerebral hemorrhage and subarachnoid hemorrhage. While all falling into the category of neurovascular emergencies, the underlying pathologies differ considerably as will the blood pressure management decisions required to treat them.

Pathophysiology

Before addressing the individual neurovascular emergencies, some underlying principles must be outlined. First, neuronal tissue has a very high metabolic demand and therefore it requires continuous high volume blood flow. Normal blood flow to the human cerebral cortex averages 50ml of blood flow / 100 grams of brain tissue / minute (expressed as: ml/100 g/min).¹ At levels of perfusion less than 20 ml/100 g/min, neuronal cell membranes become impaired with resulting neurological dysfunction.¹ Despite this impairment, if blood flow is eventually restored, this tissue is largely salvageable. At levels of blood flow below 10 ml/100 g/min, the neuronal tissue rapidly becomes irreversibly damaged. In the no-flow state, neuronal death begins within a few minutes. Thus, any attempts to alter neurovascular



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physiology must be performed with the principle of maintaining adequate cerebral blood flow to maintain tissue viability.

Without superimposed pathology, the two principal factors that affect the volume of cerebral blood flow are the cerebral perfusion pressure (CPP) and the brain's autoregulatory system. Cerebral perfusion pressure is the mean arterial pressure (MAP) minus either the intracerebral pressure (ICP) or the central venous pressure (CVP), whichever is higher.

CPP = MAP – (ICP or CVP, whichever is greater)

The native autoregulatory system refers to the brain's ability to keep the cerebral blood flow at a relatively constant level over a wide range of CPP. This is accomplished by varying the resistance in the pre-capillary arterioles.² Notably this mechanism is functional over a very wide

range of CPP (Figures 1).² Also note in this figure that a second curve depicts the autoregulatory curve "shifted" to the right. This curve represents the autoregulatory range of the patient with significant underlying hypertension. For chronically hypertensive patients, the native system will require higher pressures to achieve the same degree of cerebral blood flow than the non-hypertensive individual.³

In the setting of neurovascular emergencies, multiple deleterious effects can ensue. First, the brain's ability to continue normal autoregulation can become compromised. This can occur due to CPP being outside of the range where autoregulation can be maintained. When CPP is below the limits of autoregulation, ischemic damage can ensue. When CPP is above the upper limit, then autoregulatory breakthrough occurs which leads to increased intracranial blood volume, increased intracranial pressure and vasogenic edema.

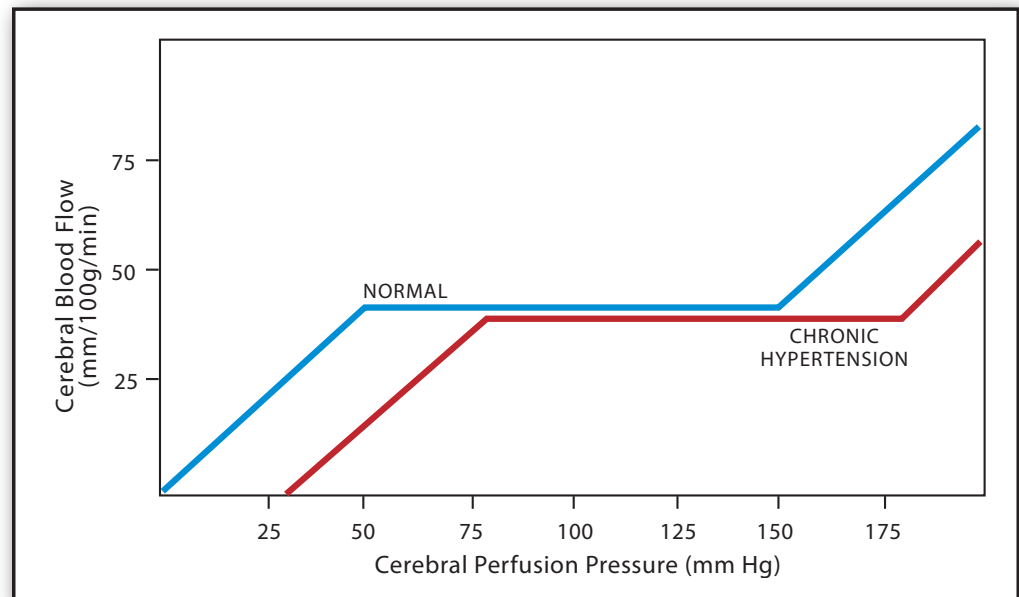
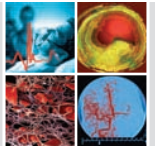


Figure 1. Auto regulation and blood flow in patients with and without chronic hypertension. Adapted with permission from Powers. Neurology 1993;43(1):461-7.



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In addition, the underlying pathology can have a significant impact on the cerebral blood flow. In the setting of an acute ischemic stroke, an arterial occlusion compromises flow to the region at risk to varying degrees depending on collateral circulation and the degree of occlusion. For intracerebral hemorrhage (ICH), the hematoma behaves as any mass lesion and causes an acute increase in ICP, thus decreasing CPP unless the MAP is also increased. It is also hypothesized that in the region immediately surrounding the hematoma the blood flow is compromised due to local physical effects of the mass lesion. For subarachnoid hemorrhage (SAH) the extravascular blood can raise ICP and can also cause arterial spasm leading to increased vascular resistance, thereby compromising flow. Thus each of the individual types of neurovascular emergencies has their own unique potential to alter blood flow.

Many factors, therefore, may influence the variable that is most important – the cerebral blood flow. In practice as emergency physicians, however, it is the systemic blood pressure over which clinicians have the greatest control and therefore it is often the primary therapeutic target. What must be considered is how treatment of the systemic blood pressure will alter the truly important variable, the cerebral blood flow, when treating patients.

Acute Ischemic Stroke

As discussed, the high metabolic demand of brain tissue makes it quite susceptible to ischemia. In the setting of acute ischemic stroke the duration and extent of ischemia will determine the ultimate fate of the affected area of brain tissue. As shown in [Figure 2](#), there is a clear relationship between duration of ischemia and level of residual blood flow that will differentiate tissue that is salvageable and that which will die.

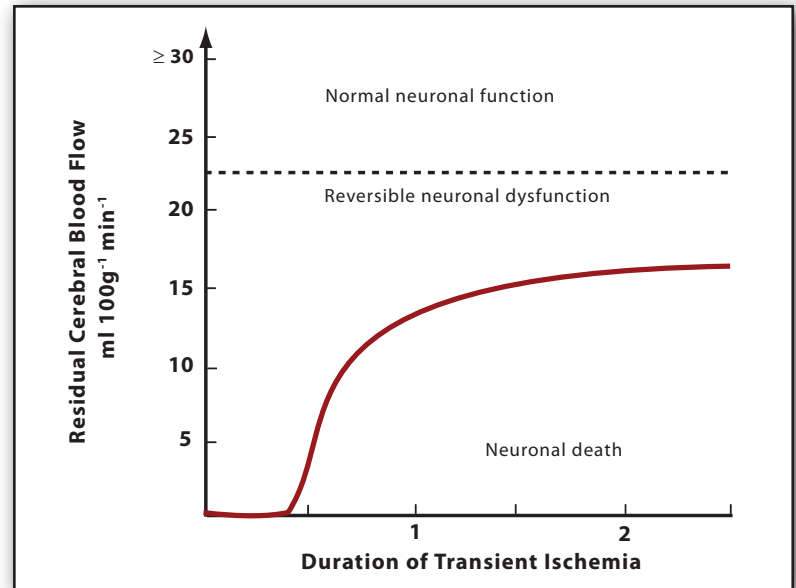


Figure 2. Degree of blood flow reduction and duration effect tissue outcome. Adapted with permission from Powers. *Neurology* 1993;43(1):461-7.

To further demonstrate the need for careful use of blood pressure medication in neurological emergencies, [Figure 3](#) illustrates the effect of blood flow on the degree of injury that can be expected in marginally perfused tissue. The centrally located black curve is adapted from Zivin who characterized neuronal injury over time in the setting of ischemia. The red and blue curves demonstrate the change in survivability that come with decreases and increases in blood flow respectively. Thus it is clear that even relatively brief periods of even relative hypotension must be avoided to prevent marked increase in injury.⁴

The best summary statement regarding blood pressure management in the setting of ischemic stroke comes from the American Stroke Association's most recent guidelines on the management of ischemic stroke. The authors state: "Despite the prevalence of arterial hypertension following stroke, its optimal management has not been established."⁵ Thus for all ischemic stroke patients, a blanket recommendation is not yet possible. Clinicians must consider what factors should influence treatment decisions and then act on a case by case basis.

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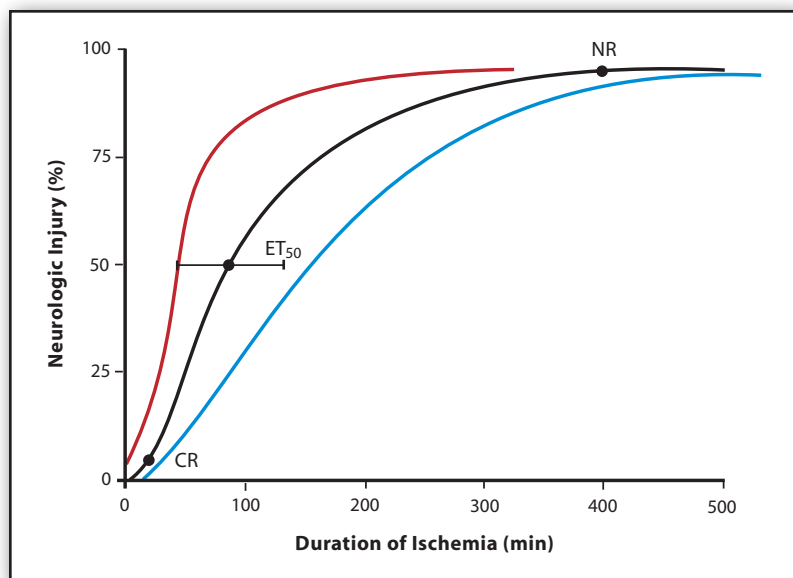


Figure 3. Degree of injury in compromised tissue based on perfusion changes. Adapted with permission from Zivin et al. *Neurology* 1998;50:599-603.

Theoretical reasons to consider lowering a patient's blood pressure include the potential to reduce the formation of brain edema, lessening the risk of hemorrhagic transformation, and preventing further vascular damage. More compelling in most patients, however, is the concern that aggressive lowering of blood pressure can cause a reduction of perfusion in the area of ischemia, which may expand the region of infarction. This is well documented in the literature with adverse clinical outcomes with sublingual nifedipine.⁶

Current expert consensus is that potential indications for acute reduction of elevated blood pressure in the setting of acute ischemic stroke include: patients who are candidates for fibrinolysis to reduce the risk of hemorrhage, patients with significant end organ damage (e.g. acute myocardial infarction, aortic dissection, hypertensive encephalopathy, acute renal failure, acute pulmonary edema, etc.), or patients with extremes of blood pressure (systolic above 220 or diastolic above 120).

The clearest indication for blood pressure lowering in the setting of acute ischemic stroke is in patients who are candidates for fibrinolytic therapy. In this population, elevated blood pressure significantly increases the risk of intracerebral hemorrhage. Fibrinolytic therapy should not be given to patients who have a systolic blood pressure >185 mm Hg or a diastolic blood pressure >110 mm Hg at the time of treatment.^{5,7} Often stroke patients arrive with very elevated blood

pressure, but it may fall within these parameters after a few minutes without specific therapy. If not, guidelines for fibrinolytic therapy allow for treatment of the blood pressure with relatively modest measures, including intravenous labetalol boluses, enalaprilat and some centers are now using nicardipine infusion. However, very aggressive interventions to lower blood pressure should not be used, so if the above measures are not effective in achieving the blood pressure targets, then fibrinolytic therapy is contraindicated. If the patient is treated with a fibrinolytic, the blood pressure must be maintained <180/105 for the next 24 hours, using any or all of the agents described below.⁷

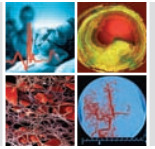
If the decision is made to treat the elevated blood pressure of a patient with acute ischemic stroke, then lowering the blood pressure should be performed *cautiously*. The agent of choice should be easily titratable to avoid erratic or precipitous declines in blood pressure and ideally would have minimal vasodilatory effect on the cerebral vessels to avoid increasing ICP. Agents with such properties include: nicardipine, labetalol, esmolol and enalaprilat. These agents are potentially useful in all of the hypertensive, neurovascular emergencies and are detailed later in this newsletter.

Intracerebral Hemorrhage

Multiple studies of ICH document an association between elevated blood pressure at presentation and poor outcomes.⁸⁻¹⁰ Data are mixed as to whether there is a relationship between elevated blood pressure at presentation and subsequent hematoma growth.¹¹ Further, studies have demonstrated that hematoma growth in ICH is a significant marker for worse outcomes.¹¹ Thus, clinicians could immediately conclude that if blood pressure is reduced, poor outcomes can be decreased either by reducing hemorrhage growth or through other factors.



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While this makes intuitive sense and may well be correct, the science to prove this hypothesis is sparse. Controversy remains as studies report conflicting conclusions. As an example, one prospective series studying hematoma growth did not find a relationship between presenting hemodynamic variables and hematoma growth.¹² Also, while lowering elevated blood pressure may seem to be a logical treatment, one study found that the more rapid the decline in MAP over the first 24 hours, the higher the mortality.¹³ Thus if the choice is made to lower blood pressure, it must be performed with extreme caution.

The final concern that has existed in the medical literature is that an area around the hematoma exists where cerebral blood flow is reduced. If this were true, then lowering the blood pressure would increase any ischemic damage in the peri-hematoma tissue. To date, however, both positron emission tomography and magnetic resonance imaging studies have not documented this phenomenon and in fact peri-hematoma autoregulation appears to be generally intact.^{14,15} Thus, this theoretical concern may not have merit and blood pressure lowering, for this purpose, is likely to be safe.

Clinicians currently have guidelines from expert consensus panels that recommend that for a patient with ICH and a history of hypertension, the MAP should be maintained less than 130 mmHg. Some clinicians, including the authors of this manuscript, believe this target may be too high, and typically aim for a MAP less than 110 mmHg in practice. For patients who have undergone craniotomy, the MAP should be maintained under 100 mmHg. In all cases, MAP should be maintained above 90 mmHg, and the CPP should be maintained above 70 mmHg.¹⁶ Physicians should also realize that pain control may significantly reduce blood pressure in these patients.

Subarachnoid Hemorrhage

Aneurysmal SAH is the one type of neurovascular emergency of which clinicians should absolutely treat elevated blood pressure. Patients with aneurysmal SAH, who do not receive definitive treatment for their aneurysm, have a risk of rebleeding of 20% at 2 weeks and 30% at one month.¹⁷ While there is little evidence

that uncontrolled blood pressure increases that risk, the potential is all too logical. Clearly, extremes of blood pressure at admission (MAP > 130 or < 70 mmHg) have been associated with poor outcomes.¹⁸ One study reports a linear relationship between early rebleeding and increasing SBP above 160 mmHg.¹⁹ Currently, most physicians caring for aneurysmal SAH treat elevated blood pressure when the patients MAP is above 130 and try to maintain the SBP below 160 mmHg. Prior to treatment with any antihypertensive agent, pain control and sedation should be considered followed by a careful reassessment of blood pressure. Agents such as fentanyl for conscious patients and propofol for patients who are intubated are excellent options. Once the decision is made to therapeutically lower blood pressure, agents that are titratable, and for SAH specifically have minimal cardiovascular side effects, such as esmolol, labetalol and nicardipine, are currently the best options.

The Agents

As previously described there are four agents that reduce blood pressure in a titratable fashion and do not lead to increases in intracranial pressure. These are nicardipine, labetalol, esmolol and enalaprilat. Each of these drugs works by different mechanisms and therefore may be of benefit to different patients.

Nicardipine

Nicardipine is a calcium ion influx inhibitor (slow channel blocker or calcium channel blocker). Nicardipine inhibits the transmembrane influx of calcium ions into cardiac muscle and smooth muscle without changing serum calcium concentrations. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. The effects of nicardipine are more selective for vascular smooth muscle than cardiac muscle. Thus, nicardipine produces a dose-dependent decrease in systemic vascular resistance. Nicardipine has been shown to be as effective as sodium nitroprusside in controlling blood pressure, but requires fewer dose titrations and does not increase ICP. It has therefore supplanted sodium nitroprusside as a treatment for acute neurovascular emergencies.

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Dosage is individualized based on the severity of the patient's hypertension and the goals for therapy. For gradual reduction in blood pressure, initiate therapy 5.0 mg/hr. If desired blood pressure reduction is not achieved at this dose, the infusion rate may be increased by 2.5 mg/hr every 15 minutes up to a maximum of 15.0 mg/hr, until desired blood pressure reduction is achieved. For more rapid blood pressure reduction, initiate therapy at 5.0 mg/hr then the infusion rate may be increased by 2.5 mg/hr every 5 minutes up to a maximum of 15.0 mg/hr, until desired blood pressure reduction is achieved. Following achievement of the blood pressure goal, the infusion rate should be decreased to 3 mg/hr. For maintenance, the rate of infusion should be adjusted as needed to achieve the desired response.

Nicardipine is contraindicated in patients with advanced aortic stenosis because part of the therapeutic effect of nicardipine is secondary to reduced afterload. Reduction of diastolic pressure in these patients may worsen rather than improve myocardial oxygen balance.²⁰

Labetalol

Labetalol is an adrenergic receptor blocking agent that has both selective α_1 - and nonselective β -adrenergic receptor blocking actions in a single drug. In humans, the ratios of α - to β -blockade have been estimated to be approximately 1:3 and 1:7 following oral and intravenous administration,

respectively. Labetalol produces dose-related falls in blood pressure without reflex tachycardia and without significant reduction in heart rate, presumably through a mixture of its α -blocking and β -blocking effects.

For hypertensive emergencies labetalol is given as either repeated intravenous boluses or as a continuous infusion. For repeat bolus dosing, labetalol injection should begin with a 10-20 mg dose (which corresponds to 0.125-0.25 mg/kg for an 80-kg patient) by IV injection over a 2-minute period. While much of the packaging of the agent lists 20 mg as the initial dose, many clinicians begin with a 10 mg dose to ensure safety of bolus therapy before proceeding to a 20 mg dose. Immediately before the injection and at 5 and 10 minutes after injection, supine blood pressure should be measured to evaluate response. Additional injections of 40 or 80 mg can be given at 10-minute intervals until a desired supine blood pressure is achieved or a total of 300 mg of labetalol has been injected. The maximum effect usually occurs within 5 minutes after each injection. A continuous infusion can also be given at 2 mg/min and titrated. The half-life of labetalol is 5 to 8 hours. In the ED, initial bolus therapy followed by infusion may be required.

Labetalol is contraindicated in bronchial asthma, overt cardiac failure, greater than first degree heart block, cardiogenic shock, severe bradycardia, and other conditions associated with severe and prolonged hypotension.²¹

Table 1. Titratable agents for hypertensive cerebrovascular emergencies

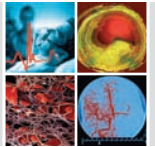
DRUG	MECHANISM	DOSE	ONSET
<i>Antihypertensives</i>			
Nicardipine	L-type CCB (dihydropyridine)	5-15 mg/h infusion	5-10 min
Labetalol	α_1 , β_1 , β_2 -antagonist	10-80 mg bolus every 10 min, up to max 300 mg; 0.5-2mg/min infusion	5-10 min
Esmolol	β_1 -antagonist	500 μ g/kg bolus, 50-300 μ g/kg/min infusion	1-2 min
Enalaprilat	ACE inhibitor	0.625 mg bolus, then 1.25-5 mg every 6 h	15-30 min

Esmolol

Esmolol is a β_1 -selective (cardioselective) adrenergic receptor blocking agent with rapid onset, a very short duration of action, and no significant intrinsic sympathomimetic or membrane stabilizing activity at therapeutic dosages. Its elimination half-life after intravenous infusion is approximately 9 minutes.



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Esmolol inhibits the β_1 receptors located chiefly in cardiac muscle, but this preferential effect is not absolute and at higher doses it begins to inhibit β_2 receptors located chiefly in the bronchial and vascular musculature.

An initial loading dose of 0.5 milligrams/kg (500 micrograms/kg) infused over a minute duration followed by a maintenance infusion of 0.05 milligrams/kg/min (50 micrograms/kg/min) for the next 4 minutes is recommended. After the 4 minutes of initial maintenance infusion (total treatment duration being 5 minutes), depending upon the desired response, the maintenance infusion may be continued at 0.05 mg/kg/min or increased step-wise to a maximum of 0.2 mg/kg/min with each step being maintained for 4 or more minutes.

Esmolol is contraindicated in patients with sinus bradycardia, heart block greater than first degree, cardiogenic shock or overt heart failure.²²

Enalaprilat

Enalaprilat, an angiotensin-converting enzyme (ACE) inhibitor when administered intravenously, is the active metabolite of the orally administered pro-drug, enalapril maleate. Enalaprilat intravenous results in the reduction of both supine and standing systolic and diastolic blood pressure. The onset of action usually occurs within fifteen minutes of administration with the maximum effect occurring within one to four hours. The duration of hemodynamic effects appears to be dose-related. Enalaprilat is indicated for the treatment of hypertension when oral therapy is not practical.

The dose in hypertension is 1.25 mg every six hours administered intravenously over a five minute period. A clinical response is usually seen within 15 minutes. Peak effects after the first dose may not occur for up to four hours after dosing. The peak effects of the second and subsequent doses may exceed those of the first.

Enalaprilat is contraindicated in patients with a history of angioedema related to previous treatment with an angiotensin converting enzyme inhibitor and in patients with hereditary or idiopathic angioedema. As with all vasodilators, enalapril should be given with caution to patients with obstruction in the outflow tract of the left ventricle.²³

Why Not Sodium Nitroprusside?

Sodium nitroprusside is used frequently in many EDs for rapid titratable blood pressure control in severely hypertensive patients. Sodium nitroprusside is a potent vascular smooth muscle relaxant, which makes this drug very attractive in the facilitation of blood pressure reduction. It is exactly this property, however, which makes the drug potentially less attractive for cases of hypertensive neurological emergencies. Of great concern in this setting is the significant potential for this agent to not only reduce systemic blood pressure via relaxation of vascular smooth muscle, but also to cause significant increases in intracranial pressure due to dilatation of intracranial vasculature via the same mechanism. This increase is nicely illustrated in **Figure 4** adapted from Anile et al. in which preoperative neurosurgical patients with intraventricular catheters

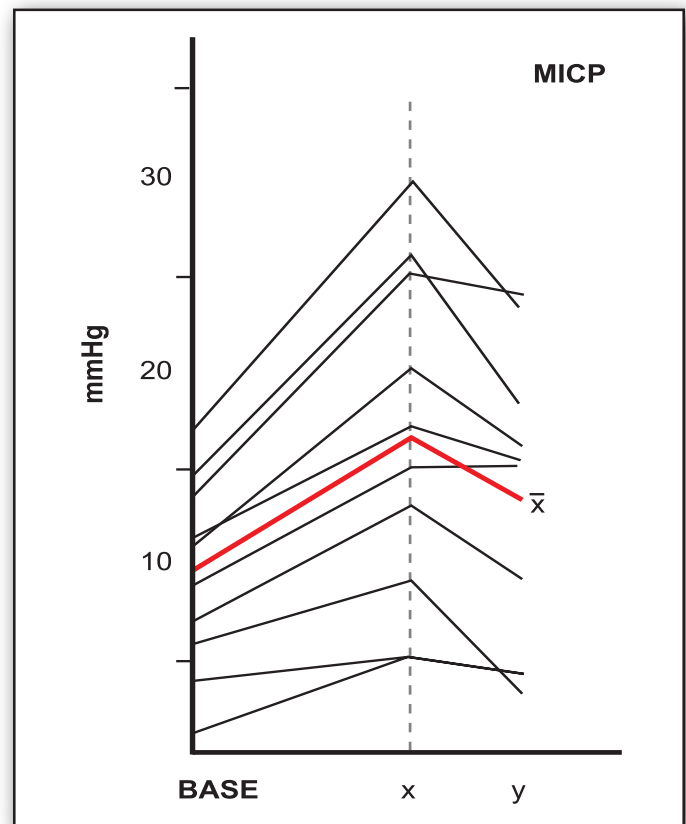


Figure 4. Changes in intracranial pressure with nitroprusside therapy. MICP = mean intracranial pressure. Adapted with permission from Anile et al. *Acta Neurochir* 1981;58:203-211.

were treated with sodium nitroprusside for blood pressure reduction. The observed increase in intracranial pressure in 9 out of 10 patients was both rapid and concerning. Notably, after an initial period of steady incremental increase in intracranial pressure, there does appear to be a phenomenon of return toward pre-treatment intracranial blood pressures. In the majority of cases, however the ICP did not return to normal and, in fact, in some cases remained markedly elevated. Thus, with multiple other powerful, titratable agents available for blood pressure control in the setting of neurovascular emergencies, the use of sodium nitroprusside is generally not recommended.²⁴⁻²⁷

SUMMARY

Blood pressure management in acute neurovascular emergencies has potential for therapeutic benefit as well as the potential to cause harm if not performed with great care. The indications for management are as yet not clearly defined and the exact degree of management is highly dependent on the individual patient and their pathology. Fortunately, highly effective and easily titratable agents exist for use with these complicated patients.

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